UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,168	08/21/2001	Jennifer L. West	002376.1017	9212

23640 7590 07/20/2009

BAKER BOTTS, LLP
910 LOUISIANA
HOUSTON, TX 77002-4995

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/20/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

debbie.allen@bakerbotts.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JENNIFER L. WEST and BRENDA K. MANN

Appeal 2009-002300
Application 09/935,168
Technology Center 1600

Decided:[1] July 16, 2009

Before TONI R. SCHEINER, DONALD E. ADAMS, and STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for making a tissue engineering scaffold. The Patent Examiner rejected the

---

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

claims as obvious, and as lacking descriptive and enabling support. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The invention concerns scaffolds for tissue engineering. (Spec. 1:4-5.) "[A]n object of the invention is to provide tissue engineering scaffolds which promote formation of ECM [extracellular matrix], to enhance the formation of tissue with good mechanical properties, on and within the tissue engineering scaffold, i.e., with little or no increase in cellular proliferation." (*Id.* at 2:25-28.) Claims 1, 2, 7, 8 and 24-35, which are all the pending claims, are on appeal.[2] Independent claims 1 and 24 are representative and read as follows:

1. A method for making a tissue engineering scaffold for inducing formation of extracellular matrix by cells bound to the scaffold comprising covalently coupling matrix-enhancing molecules to the scaffold in an effective density to elicit production of extracellular matrix without increasing cellular proliferation, wherein when the matrix-enhancing molecules are TGF-β, the TGF-β is covalently coupled to the matrix by a polymer tether having a molecular weight between 2000 and 6000 and is in a density between 1 and 100 ng TGF-β/ml or in a concentration of between about 4×10^{-6} and 4×10^{-3} nmol/ml.

24. A method for making a tissue engineering scaffold, the method comprising:

---

[2] The Examiner cancelled claims 3-5 and 9 in a communication mailed Sept. 29, 2008.

providing a scaffold, a polymer tether, and a matrix-enhancing molecule;

covalently coupling the polymer tether to the scaffold; and covalently coupling the matrix-enhancing molecule to the scaffold, wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell.

These are the appealed rejections:

• claims 24-35 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure in scope with the claims;

• claims 24-35 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;

• claims 1, 2, 4 and 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee[3] and Dinbergs;[4]

• claims 7 and 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee, Dinbergs and Schinstine;[5]

• claim 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Dinbergs and either of Bentz[6] or Cima;[7]

---

[3] U.S. Patent No. 5,162,430, issued to Woonza Rhee et al., Nov. 10, 1992.
[4] Iveta D. Dinbergs et al., *Cellular Response to Transforming Growth Factor-β1 and Basic Fibroblast Growth Factor Depends on Release Kinetics and Extracellular Matrix Interactions*, 271 J. BIOL. CHEM. 29822-29 (Nov. 1996).
[5] U.S. Patent No. 5,935,849, issued to Malcolm Schinstine et al., Aug. 10, 1999.
[6] WO 94/23740, by Johanna Bentz et al., published Oct. 27, 1994.
[7] WO 96/27657, by Linda G. Cima et al., published Sep. 12, 1996.

• claims 24-27 and 32-34 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Schinstine;

• claims 27 and 29 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee, Schinstine and Dinbergs;

• claims 24 and 30 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Scott-Burden;[8] and

• claims 24 and 34 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and either of Bentz or Cima.

ENABLEMENT

The Enablement Issue

The Examiner's position is that the Specification "does not teach how to make all 'matrix-enhancing molecule[s]' covalently coupled to a polymer tether for the claimed method without the amino acid sequence of 'matrix-enhancing molecule[s].'" (Ans. 5.) "Given the unlimited number of matrix enhancing molecules and without the structure (i.e. chemical structure of amino acid sequence) and these matrix enhancing molecules have different effects on different cell type[s], it is unpredictable which undisclosed matrix-enhancing molecule and at which concentration is effective for inducing which matrix production for the claimed method with [sic] further guidance from the [S]pecification." (*Id.*)

---

[8] Timothy Scott-Burden, *Modulation of Extracellular Matrix by Angiotensin II: Stimulated Glycoconjugate Synthesis and Growth in Vascular Smooth Muscle Cells*, 16(Suppl. 4) J. CARDIOVASC. PHARMACOL. S36-S41 (1990).

Appellants contend that the Examiner misconstrued the Specification to define matrix-enhancing molecule as "any glycoproteins." (App. Br. 9.)[9] According to Appellants, matrix-enhancing molecules are well known and the Specification need not disclose what is well known. (*Id.* at 10.) "[E]ach element of the claim identified by the [E]xaminer represents well-known subject matter that the [S]pecification nevertheless explains and exemplifies." (*Id.*) Appellants argue that the prior art cited by the Examiner discloses matrix-enhancing molecules, extracellular matrix materials, and cell types. (*Id.* at 11-12.) Appellants contend that the experimentation required to determine appropriate operating concentrations is not undue in view of the examples given and the fact that those of skill in the art "typically engage in some degree of experimentation." (*Id.* at 14-15.)

The issues with respect to this rejection are

Did the Appellants' failure to provide "all" amino acid sequences for matrix-enhancing molecules compel a conclusion of non-enablement;

Did the rejection give appropriate weight to the state of the prior art; and

Did the rejection give appropriate weight to the amount of direction or guidance provided?

Findings of Fact Relating to Enablement

1. The Specification taught that the optimal density of the matrix-enhancing molecule to elicit ECM production without promoting

---

[9] Citations are to the "Amended Appeal Brief" dated Jan. 31, 2007.

cellular proliferation "will depend on the type of cells to be attached to the scaffold." (Spec. 7.)

2. The Specification listed TGF-β, angiotensin II, insulin-like growth factors and ascorbic acid as suitable matrix-enhancing molecules. (Spec. 6:10-11.)
3. The Specification provided working examples using TGF-β. (Spec. 6: 8-15.)
4. The Specification provided a working example using ascorbic acid. (Spec. 15.)
5. Rhee disclosed matrix-enhancing molecules including TGF-β, epidermal growth factor, and insulin-like growth factors. (Ans. 8, citing col. 6, ll. 55-66.)
6. Rhee taught that when using growth factors to stimulate tissue growth with a scaffold-type implant, the amount of growth factor to incorporate and the rate of delivery "may easily be determined by routine experimentation." (Col. 13, ll. 9-17.)
7. Dinbergs disclosed matrix-enhancing molecules basic fibroblast growth factor (bFGF) and transforming growth factor-β1 (TGF-β1). (Ans. 9, citing p. 29823.)
8. Schinstine disclosed matrix-enhancing molecules. (Ans. 11, citing col. 18 and col. 12.)
9. Scott-Burden disclosed that angiotensin II was a matrix enhancing molecule. (Ans. 10, citing p. S96 [sic].)

Principles of Law Relating to Enablement

A lack of enablement rejection is appropriate where the written description fails to teach those in the art to make and use the invention as broadly as claimed without undue experimentation. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). "The PTO cannot make this type of rejection, however, unless it has reason to doubt the objective truth of the statements contained in the written description." *Id.*, 165 F.3d at 1357.

"[A]pplicants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art." *In re Angstadt*, 537 F.2d 498, 503 (CCPA 1976) (emphasis in original).

Analysis of the Enablement Issue

First, the fact that the Specification did not recite amino acid sequences for "all" matrix-enhancing molecules is not enough, taken alone, to compel a conclusion of non-enablement. The law does not require disclosure of "*every* species encompassed by [the] claims even in an unpredictable art." *Angstadt*, 537 F.2d at 503 (emphasis in original). Instead, a conclusion of nonenablement is reached by weighing a number of factual findings.[10] It was error to require a disclosure of "all" structures

[10] Facts that should be considered in determining whether a specification is enabling, or if it would require an undue amount of experimentation to practice the invention include: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of

without an explanation why the circumstances justified the requirement in the context of the *Wands* factors.

Second, Appellants point to evidence in the record that many matrix-enhancing molecules were known in the prior art, and that a variety of scaffold materials were known in the prior art. (App. Br. 11.) According to Appellants, the references Rhee, Dinbergs, Schinstine, and Scott-Burden all disclose matrix-enhancing molecules in addition to TGF-β. (*Id.*) The Examiner relied on the same disclosures as evidence of the scope and content of the prior art in the obviousness analysis, but apparently gave them no weight when considering the state of the prior art for purposes of enablement. It was error to reach a conclusion of nonenablement without weighing all the record evidence on the state of the prior art.

Third, the Specification described how to assess the amount of growth factor needed to elicit production of ECM without increasing cellular proliferation. The Specification provided additional guidance in working examples with TGF-β and with ascorbic acid. The Examiner doubted that other matrix enhancing molecules would produce similar results (Ans. 5), but gave no factual basis for doubting the Specification's teachings that other molecules would work. *See Cortright*, 165 F.3d at 1357 (the Office must provide a reason to doubt objective statements in the Specification). The Examiner also found that working concentrations would be unpredictable (Ans. 5), but gave no explanation why that factor alone was

---

the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

enough to conclude that persons of ordinary skill in the art would be incapable of following the Specification's teachings. Appellants' contention that persons of ordinary skill in this art are accustomed to some experimentation (App. Br. 14) is unrebutted, and their contention appears to be consistent with teachings in the prior art of record. (FF6.) The Specification provided guidance, but the Examiner did not provide objective evidence that the guidance was insufficient, beyond a general assertion of unpredictability.

We conclude that the available evidence of record on the relevant *Wands* factors is insufficient to support an enablement rejection.

WRITTEN DESCRIPTION

The Written Description Issue

The Examiner's position is that the Specification "does not reasonably provide a written description of any matrix-enhancing molecule, the concentration of any such matrix-enhancing molecule such as angiotensin II, insulin like growth factor other than TGF-β and ascorbic sufficient to elicit production of any extracellular matrix by any cell attached to any engineering scaffold." (Ans. 6, emphasis deleted.) One of ordinary skill in the art would not find the Specification's examples with TGF-β and ascorbic acid "to provide a representative number of species of matrix-enhancing molecule and the concentration for all matrix enhancing molecule to describe the genus for the claimed method." (*Id.* 7-8.)

Appellants contend that "[t]he Examiner's requirement that all matrix-enhancing molecules must be reported in the [S]pecification is clear error."

(App. Br. 17.) According to Appellants, the Specification describes matrix-enhancing molecules, and "the prior art cited by the Examiner shows that suitable matrix-enhancing molecules are well known." (*Id.* at 17-18.)

Appellants further contend that extracellular matrix, cells attached to the scaffold, and scaffolds, were described. (*Id.* at 18-20.) Appellants summarize their own structure-function correlation argument as follows: "the matrix-enhancing molecule, a class of molecule both well-known in the art and described generically and by example in the [S]pecification, is covalently coupled to the scaffold through a tether. This tethered matrix-enhancing molecule retains the function of the untethered matrix-enhancing molecule, to increase the production of extracellular matrix by cells." (*Id.* at 20.)

The issues with respect to this rejection are:

Must Appellants disclose "all" matrix-enhancing molecules to describe the generic method;

Must Appellants disclose the working concentrations of "all" matrix-enhancing molecules to describe the generic method;

Were working examples with TGF-β and ascorbic acid a "representative number" describing the generic method; and

Did the prior art cited by the Examiner show that suitable matrix-enhancing molecules were well known?

Findings of Fact Relating to Written Description

We rely on findings 1-9.

Principles of Law Relating to Written Description

When an Applicant claims a class, the Applicant "must describe that class in order to meet the description requirement of the statute." *In re Lukach*, 442 F.2d 967, 968 (CCPA 1971). The amount of description needed to meet the requirement can vary with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). General knowledge in the art has the effect of expanding the description in a patent application. *In re Alton*, 76 F.3d 1168, 1175-76 (Fed. Cir. 1996).

Analysis of the Written Description Issue

The requirement that Appellants provide an amino acid sequence for every matrix-enhancing molecule was not supported by a reasoned explanation. The written description requirement "states that the patentee must describe the invention; it does not state that every invention must be described in the same way." *Capon*, 418 F.3d at 1358. Appellants point to prior art disclosures of a number of matrix-enhancing molecules as evidence that such molecules were known in the art. This pre-existing knowledge in the art adds to the Specification's disclosures. *Alton*, 76 F.3d at 1175-76. Taking account of the evidence that additional molecules were known to those of ordinary skill in the art, we are not persuaded that all the evidence of record supports a requirement for additional "representative" examples.

The explanation of the rejection uses the term "any" to indicate what is missing. For example, the disclosure is faulted for not disclosing "any matrix-enhancing molecule, the concentration of any such matrix-enhancing

molecule such as angiotensin II, insulin like growth factor other than TGF-β and ascorbic sufficient to elicit production of any extracellular matrix by any cell attached to any engineering scaffold." (Ans. 6.) An ordinary meaning of any is "one, a, an or some." A finding that not one matrix-enhancing molecule was disclosed is plainly wrong, because the Specification named several; and the working examples disclosed operating concentrations for two of the molecules. However, we recognize that "any" can also mean "every." We conclude the Examiner meant that not "every" matrix-enhancing molecule was disclosed, and that no concentrations other than those for TGF-β and ascorbic acid operating on the exemplified cells were disclosed. That may be so, but it is not enough to answer the question whether those of skill in the art would accept Appellants' claim to possession of a generic invention.

On that question, the written description requirement and the enablement requirement are similar: "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon*, 418 F.3d at 1359 (a "written description" case), citing *Angstadt* (an "enablement" case). Appellants' Specification taught that low concentrations or densities of matrix-enhancing molecules elicit production of ECM without increasing cellular proliferation. (FF1.) Working examples demonstrated the effect with TGF-β and with ascorbic acid, two structurally distinct molecules. (FF 2) The question is whether "the effect is sufficiently demonstrated to characterize a generic invention."

The rejection acknowledges the Specification's two demonstrations, but requires more because the art is "unpredictable." We accept the Examiner's finding that this art was unpredictable. However, the disclosure that two structurally distinct growth factors behaved similarly does not weigh in favor of finding that other growth factors would behave differently. The generalized concept of unpredictability must give way to the objective evidence of predictability that Appellants presented. The rejection does not persuade us that those of skill in the art would require more than the Specification and the general knowledge in the art to be persuaded that Appellants had possession of a generic invention.

OBVIOUSNESS

The Obviousness Issue

Appellants contest seven obviousness rejections of the various claims. In each rejection, the teachings of Rhee were combined with one or more other references. The Examiner's common position in each rejection is that Rhee taught nearly every element of the claimed methods, but for one or two elements taught or suggested by each of the other references.

Regarding the combination of teachings from Rhee and Dinbergs, Appellants contend that (i) "there is no reason, suggestion, or motivation to combine the references in the manner required to produce the claimed invention," (ii) the "rejection is premised on a flawed understanding of *Dinbergs*," and (iii) no reference teaches "an effective density to elicit production of extracellular matrix without increasing cellular proliferation." (App. Br. 25.)

Regarding the combination of teachings from Rhee and Schinstine, Appellants contend that (i) "the Examiner has improperly construed the scope of claim 24," (ii) "there is no reason, suggestion, or motivation to combine the references in the manner required to produce the claimed invention," and (iii) the method resulting from the combination "would not include every limitation recited in Applicants' independent claim 24." (App. Br. 44.)

Regarding the combination of teachings from Rhee and Scott-Burden, or Rhee and Bentz, or Rhee and Cima, Appellants contend (i) "there is no reason, suggestion, or motivation to combine the references in the manner required to produce the claimed invention," and (ii) the method resulting from the combination "would not include every limitation recited in Applicants' independent claim 24." (App. Br. 48 and 50.)

The issues with respect to the obviousness rejections are:

Did the evidence support a reason, suggestion or motivation to combine the references in a manner that would have produced the claimed method;

Did the Examiner have a flawed understanding of Dinbergs;

Did any reference teach "an effective density to elicit production of extracellular matrix without increasing cellular proliferation;"

Did the Examiner misconstrue claim 24; and

If the teachings of Rhee were combined with those of Schinstine, Scott-Burden, Bentz, or Cima, would their combined methods produce the claimed invention?

Findings of Fact Relating to Obviousness

Rhee

10. Rhee described a collagen-polymer conjugate. (Col. 4, ll. 5-7.)

11. Rhee taught using the composition as an implant with factors such as TGF-β to "aid in the healing or regrowth of normal tissue." (Col. 6, ll. 53-66.)

12. Rhee disclosed that "[b]y tethering factor molecules to the implant, the effective amount of the factor is substantially reduced." (Col. 7, ll. 8-10.)

12. Rhee defined "effective amount" as "the amount of composition required in order to obtain the effect desired. Thus, a 'tissue growth promoting amount' of a composition containing a growth factor refers to the amount of factor needed in order to stimulate tissue growth to a detectable degree." (Col. 7, ll. 15-20.)

14. Rhee taught that growth factors such as EGF or TGF-β were "preferably provided at a concentration of about 1 μg/mL to about 5 mg/mL." (Col. 10, ll. 65-67.)

Dinbergs

15. Dinbergs "examined basic fibroblast growth factor (bFGF) and transforming growth factor-β1 (TGF-β1) release kinetics from synthetically fabricated microsphere devices and naturally synthesized extracellular matrix." (Abstract.)

16. Dinbergs reported on "Cell Proliferation Assays" done with two different kinds of control release devices: alginate/heparin-Sepharose

controlled release microspheres with bFGF, and ethylene-vinyl acetate copolymer-TGF-β1 controlled release microspheres. (29823:para. bridging cols. 1-2.)

17. Controlled release of bFGF via a microsphere device provided optimal endothelial and smooth muscle cell proliferation compared to bolus administration, measured as an increase in cell number. (Fig. 2, legend.)

18. Bolus administration of TGF-β1 produced maximal inhibition of endothelial and smooth muscle cell proliferation, compared to controlled release via a microsphere device. (Fig. 3, legend.)

19. "The controlled release of TGF-β1 from an EVAc-BSA-TGF-β1 microsphere did not demonstrate a statistically significant effect on [smooth muscle] cell growth." (29825, right col., 1st para.)

Schinstine

20. Schinstine's disclosure related to "methods and compositions of controlling cell distribution within a bioartifical organ [BAO] by exposing cells to a treatment that inhibits cell proliferation, promotes cell differentiation, or affects cell attachment to a growth surface within the bioartificial organ." (Abstract.)

21. Schinstine taught that "[t]he core of the BAO is constructed to provide a suitable local environment for the particular cells isolated therein." (Col. 20, ll. 42-43.)

22. Schinstine disclosed that cytokines including TGFβ1 "may be used to arrest or inhibit cell proliferation or to induce cell differentiation." (Col. 12, ll. 57-59.)
23. Schinstine's "Table 1" provided "a partial list of ECM molecules[,] growth factors and chemical compounds known to influence proliferation and differentiation in particular cell types." (Col. 15, ll. 65-67; *see* Table 1 at col. 16.)

Scott-Burden

24. Scott-Burden reported that angiotensin II "was capable of stimulating both growth and matrix elaboration by cultured vascular smooth muscle cells." (Abstract.)
25. Scott-Burden's "Results" section reported that when vascular smooth muscle cells were maintained for 12 days in the presence of angiotensin II, morphological changes "could be correlated with the onset of full extracellular matrix production" and "the number of cells in wells exposed to 10^{-7} M [angiotensin II] was 2.5 x 10^{6} cells/well, as compared to 10^{6} cells/well for control." (S37-S38, 1st full para. in "Results".)

Bentz

26. Bentz taught stimulating bone formation by administering an effective amount of a conjugate of a growth factor and a hydrophilic polymer. (Abstract.)

27. Bentz taught that the conjugate, such as TGF-β and polyethylene glycol, "can stimulate bone formation at lower dose levels at which the growth factor, unmodified, is ineffective." (*Id.*)

Cima

28. Cima taught gowth effector molecules flexibly tethered to a solid substrate. (Abstract.)
29. Cima taught that "[this] method can be used as a means of enhancing the therapeutic use of growth factors *in vivo* and of creating surfaces which will enhance *in vitro* growth of difficult-to-grow cells such as liver cells." (*Id.*)
30. Cima's growth effector molecules included EGF, PDGF, TGFα, TGFβ, hepatocyte growth factor, heparin binding factor, fibroblast growth factor, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, "and other factors known to those of skill in the art." (10:20-29.)

Principles of Law Relating to Obviousness

Obviousness is a question of law based on fact findings. The scope and content of the prior art are determined; differences between the prior art and the claims at issue are ascertained; the level of skill in the art is resolved; and objective record evidence of nonobviousness is considered. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). A rejection for obviousness must include "articulated reasoning with some rational underpinning to support

the legal conclusion." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

The proper question to ask is whether a person of ordinary skill in the art, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424; *see also In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (the desirability of the combination may arise from nature of the problem, teachings of references, or the ordinary knowledge of those skilled in the art).

Analysis of the Obviousness Issue

Each of the obviousness rejections is based on the teachings of Rhee in combination with one or more other references. Rhee taught a method for making a tissue engineering scaffold comprising covalently coupling TGF-β via polymer tether to a scaffold. Rhee reported an increase in cell proliferation, but did not report on ECM production. The Examiner found that claim 1 differed from Rhee's tissue-scaffold method in that Rhee used TGFβ at a concentration of about 1 μg/ml to about 5 mg/ml, but the claim recites a TGFβ density between 1 and 100 ng/mL. (Ans. 9.) Put another way, Rhee's TGFβ concentrations were from ten to five thousand times higher than Appellants claim.

The fundamental dispute in this appeal is whether the prior art suggested using lower concentrations of growth factor in Rhee's method. Appellants' argument is essentially that they discovered that lower growth factor concentrations have the unexpected benefit of increasing ECM production without increasing cell proliferation. According to the

Specification, that result is beneficial because it enhances the formation of tissue with good mechanical properties, on and within the tissue engineering scaffold. (Spec. at 2:25-28.)

Claim 1 and its dependent claims

In a first set of rejections directed to claim 1 and its dependent claims, the Examiner relied on the combination of Rhee with Dinbergs as suggesting the claimed method using TGFβ in the ng/ml range. The Examiner found that Dinbergs' microsphere method was a tissue engineering scaffold method that used TGFβ at 1-10 ng/ml. The Examiner also found: "[t]he reference TGFβ is effective to elicit production of extracellular matrix (see 29822, column 2, last paragraph, in particular) without increasing cellular proliferation (See Fig 2B, Fig 3B, Abstract, in particular)." (Ans. 9.) We next look at each of the referenced parts of Dinbergs.

We first note that Dinbergs' Abstract does not indicate that any measurements of ECM production were made during the work reported. Dinbergs at page 29822, last paragraph, mentions previous reports that bFGF and TGFβ "have profound and sustained mediation of" extracellular matrix accumulation. The paragraph goes on to report Dinbergs' own results measuring cell proliferation, but does not mention a measurement of ECM production. Dinbergs' Figs. 2B shows that bFGF administered via controlled release microsphere resulted in an increase in smooth muscle cell number, compared to the control. Fig. 2B does not report an ECM measurement. Fig. 3B displays plots recording increases in smooth muscle cell number on exposure to TGF-β1. Fig. 3B does not report ECM measurement. In Fig. 3B the control was plotted with an open circle (○),

and the microsphere treated cells were plotted with a filled circle (●). The plots are virtually congruent. According to the text, the controlled release microsphere did not have a statistically significant effect on cell growth. (FF16.) Thus, the treatment with ng range TGF-β1 did not cause an increase in cellular proliferation over the control or normal proliferation.

After reviewing the passages in Dinbergs that the Examiner referred to, we find no explicit support for the Examiner's finding that "[t]he reference TGFβ is effective to elicit production of extracellular matrix . . . without increasing cellular proliferation . . . ." The Examiner argues that "production of extracellular matrix is an inherent property of TGF-β." (Ans. 34, citing the Specification and references). There is, however, no evidence that a person of ordinary skill in the art was aware of a concentration range at which the inherent activity of eliciting ECM production would be active, but the inherent activity of promoting cellular proliferation would be inactive. There is no evidence that a person of ordinary skill in the art perceived that a benefit would result from modifying Rhee's method with Dinbergs' concentrations.

The fact that something inherent would result from a combination of prior art is not the same as evidence that the combination was suggested by the prior art. The invention would not have been obvious unless a person of ordinary skill in the art "would have seen a benefit to combining the prior art teachings." *KSR*, 550 U.S. at 424. On this record, inherency did not supply the reason a person would have seen a benefit to combining the prior art teachings. If a reason to make the modification had been present, an inherent result may not make the claim nonobvious, but that is not the case

here because the Examiner has not established an independent reason for the modification. *Contrast with In re Kubin*, 561 F.3d 1351, 1357-58 (the prior art suggested the composition independently of an inherent feature); *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979) (rejecting the notion that "a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable ... because it also possesses an inherent, but hitherto unknown, function which [Applicants] claim to have discovered."). In *Kubin* and *Wiseman*, the inventions were suggested by the prior art for reasons separate from the inherent properties of the claimed composition and device, respectively. We do not agree with the Examiner's further finding that "Dinbergs *et al* teach TGFβ is useful for eliciting extracellular matrix formation without increasing cellular proliferation for up to five days . . . ." (Ans. 10.) The reason the Examiner gave for modifying the Rhee method to use Dinbergs' TGFβ concentration is not supported by the evidence. We therefore reverse the rejections of claim 1 and its dependent claims based on the combination of Rhee with Dinbergs.

Claim 24 and its dependent claims

Claim 24 is drawn to a method for making a tissue engineering scaffold, with a matrix-enhancing molecule covalently coupled to the scaffold, "wherein the matrix-enhancing molecule is present at a concentration sufficient to elicit production of extracellular matrix by a cell attached to the tissue engineering scaffold without increasing cellular proliferation of the attached cell."

In a set of rejections directed to claim 24 and its dependent claims, the Examiner again relies first on Rhee. In the first rejection of the set, rejecting claims 24-27 and 32-34 over Rhee and Schinstine, the Examiner did not address the claimed concentration of matrix-enhancing molecule in the rejection. (Ans. 14-16.) That is, the Examiner did not identify prior art that taught or suggested the particular concentration, did not identify the concentration as different from the prior art, and did not offer a reason why the particular concentration would have been obvious. We reverse this rejection because it did not account for all the claim limitations.

In a later discussion section, the Examiner argued that adjusting concentrations is within the skill in the art or may easily be determined by routine experimentation. (Ans. 57.) In the Examiner's view, the burden was shifted to Appellants "to show that the prior art method is different from the claimed method." (*Id.*, citing *In re Best*.) However, none of the cited references provide guidance to the claimed concentration. On this record, the art was not informed of guidance for adjusting the concentration to elicit ECM production without increasing cellular proliferation until Appellants filed their Application. There is no evidence that any of the prior art methods were the same as that claimed. There is no evidence that routine adjustment for the purpose of increasing cellular proliferation, the purpose of every cited prior art reference, would have been likely to arrive at the claimed concentration that does the opposite. We do not agree that the evidence was enough to shift the burden under *Best*.

The remaining rejections directed to claim 24 or its dependent claim, combining Rhee with Scott-Burden, Bentz, or Cima, applied the same

reasoning to the claimed concentration. We reverse those rejections because they do not account for all the claim limitations.

CONCLUSIONS OF LAW

Enablement

Appellant's failure to provide "all" amino acid sequences for matrix-enhancing molecules did not compel a conclusion of non-enablement; and the Answer's *Wands* analysis did not give appropriate weight to the state of the prior art and to the amount of direction or guidance provided in the Specification. We conclude that the factual analysis set out in the Answer is insufficient to support a conclusion of nonenablement.

Written Description

The law did not require Appellants to disclose "every" matrix enhancing molecules to describe the generic method, nor did it require Appellants to disclose the working concentration of "every" matrix enhancing molecules to describe the generic method. We agree with Appellants that the prior art cited by the Examiner showed that suitable matrix-enhancing molecules were well known. The Examiner did not did establish why more working examples should be required. We find that the two demonstrations with TGF-β and ascorbic acid were a "representative number" sufficient to characterize a generic method. We find the evidence of record insufficient to support the written description rejection.

Obviousness

The evidence did not support a reason, suggestion or motivation to combine the references in a manner that would have produced the claimed method;

Dinbergs did not disclose that a ng/ml concentration of TGF-β elicited ECM production without increasing cellular proliferation;

None of the references taught "an effective density to elicit production of extracellular matrix without increasing cellular proliferation;"

The Examiner did not establish that the combined teachings of Rhee and Dinbergs rendered the methods of claim 1 and its dependent claims obvious; and

The Examiner did not establish that the combined teachings of Rhee, Schinstine, Dinbergs, Scott-Burden, Bentz, or Cima, rendered the methods of claim 24 and its dependent claims obvious.

SUMMARY

We reverse the rejections of

claims 24-35 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure commensurate in scope with the claims;

claims 24-35 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;

claims 1, 2, 4 and 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Dinbergs;

claims 7 and 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee, Dinbergs and Schinstine;

claim 8 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Dinbergs and either Bentz or Cima;

claims 24-27 and 32-34 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Schinstine;

claims 27 and 29 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee, Schinstine and Dinbergs;

claims 24 and 30 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and Scott-Burden; and

claims 24 and 34 under 35 U.S.C. § 103(a) as obvious over the combined teachings of Rhee and either Bentz or Cima.

REVERSED

Ssc:

BAKER BOTTS LLP
910 LOUISIANA
HOUSTON, TX 77002-4995